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Meta-analyses

Effects of vitamin D on serum lipid profile in patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: The effect of vitamin D on lipid profile in type 2 diabetic patients is controversial. This meta-analysis aimed to assess the effect of vitamin D on serum total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) of these patients to elucidate the subject.

Methods: Seven databases were searched and randomized controlled trials (RCTs) assessed the effect of vitamin D on lipid profile published until November 2015 were identified. Un-standardized mean difference and its corresponding 95% confidence interval (CI) was calculated from the effect sizes by using random effects model.

Results: We found 2220 articles in our systematic search, after exclusion of un-related studies we enrolled 17 studies comparing intervention group (received vitamin D) with control group (received placebo) in the meta-analysis. Vitamin D significantly reduced serum TC (−3.74 mg/dl, 95% CI: −7.13 to −0.34, $P = 0.031$), but serum TG did not show significant reduction (−4.90 mg/dl, 95% CI: −15.11−5.31, $P = 0.347$). Results confirmed the significant lowering effect of vitamin D on LDL in patients with T2D (−2.55 mg/dl, 95% CI: −4.83 to −0.26, $P = 0.029$), but change in serum HDL was negligible (−0.72 mg/dl, 95% CI: −1.27 to −0.17, $P = 0.010$). Subgroup analyses showed that the baseline serum 25-hydroxy vitamin D of patients, vitamin D dosage, intervention duration, and the method of vitamin D application influence the effect of vitamin D on lipid markers.

Conclusion: This study demonstrated that vitamin D improved serum levels of TC, TG, and LDL in patients with T2D but changes of serum HDL was not satisfactory.

1. Introduction

Type 2 diabetes (T2D) is one of the main causes of morbidity and mortality throughout the world. It is estimated that up to 2035, more than 600 million patients would suffer from the disease [1]. The related annual therapeutic and rehabilitative costs of diabetes are onerous. A great deal of the health-related expenditures are dedicated to diabetes and its complications [2].

Vitamin D was discovered in 1928 and for years was known as an essential factor for bone growth and calcium homeostasis. Beyond the skeletal effects, the presence of vitamin D receptors in other tissues and organs illustrates its extra-skeletal effects like modulation of immune function and inflammation, insulin secretion, cardiovascular protection, and gene expression [3,4].

Vitamin D deficiency and insufficiency as a worldwide problem is related to chronic diseases such as diabetes, metabolic syndrome, and cardiovascular diseases [3,5]. Serum levels of 25-hydroxy vitamin D (25OHD) is used to determine the vitamin D status. The most acceptable definition introduced by the Endocrine Society states Serum levels of 25OHD <50, 50−74, and >75 nmol/l as deficient, insufficient, and sufficient, respectively [6].

It is demonstrated that low-grade inflammation and autoimmune activation play important roles in development and progression of T2D. Increased activity of inflammatory cytokines induces beta-cell apoptosis in the pancreas and increases insulin

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resistance in target cells which are the main pathogenesis of diabetes. Regarding anti-inflammatory effects of vitamin D and the fact that diabetes is more prevalent in vitamin D deficient subjects, vitamin D has been used in clinical trials for diabetic patients [3,7,8]. Cardiovascular events are common problem in diabetic subjects and as one of the major causes of morbidity and mortality require precise interventions. Dyslipidemia is known as a potential risk factor for cardiovascular events and must be managed carefully [9]. Dyslipidemia is also common in patients with T2D. Moreover, observational studies declared that subjects with high serum 25OHD have acceptable levels of lipid markers [10].

The effect of vitamin D on lipid profile of diabetic patients is considered in some clinical trials; however, the results are controversial. This meta-analysis aimed to assess the effect of vitamin D on lipid profile of patients with T2D to elucidate the subject.

2. Materials and methods

2.1. Review design and search strategy

The protocol was registered in PROSPERO, the international database of registered systematic reviews (registration number: CRD42015027867). The PRISMA guidelines were followed for performing and reporting the results of this meta-analysis [11]. Seven databases including PubMed, Cochrane register of control trials, ISI Web of Science, Scopus, Google Scholar, Magiran, and Iran Medex were searched and randomized controlled trials (RCTs) published until November 2015 were identified.

Pubmed was searched with the search strategy as follows: ("Cholecalciferol"[Mesh] OR "Calcitriol"[Mesh] OR "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "vitamin D2"[tiab] OR "vitamin D3"[tiab] OR "vitamin D-") AND ("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabetes"[tiab] OR "diabetic"[tiab] OR "diabetes"[tiab]) AND ("Intervention Studies"[MESH] OR "intervention"[tiab] OR "controlled trial"[tiab] OR "randomized"[tiab] OR "randomised"[tiab] OR "random"[tiab] OR "randomly"[tiab] OR "placebo"[tiab] OR "assignment"[tiab] OR "clinical trial"[All Fields] OR "trial"[All Fields]). The search strategy for ISI Web of Science was: ("Cholecalciferol" OR "Calcitriol" OR "Vitamin D" OR "Ergocalciferols" OR "vitamin D2" OR "vitamin D3" OR "vitamin D-") AND ("Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "type 2 diabetes" OR "diabetic" OR "diabetes") AND ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "clinical trial" OR "trial"). Scopus was searched with: "Cholecalciferol" OR "Calcitriol" OR "Vitamin D" OR "Ergocalciferols" OR "vitamin D2" OR "vitamin D3" OR "vitamin D-" AND "Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "type 2 diabetes" OR "diabetic" OR "diabetes" AND "Intervention Studies". The other databases were searched by the key words: "vitamin D" AND "diabetes". Titles, abstracts, and if necessary full text of the studies were separately evaluated by authors to identify the related studies. Moreover, a hand-search was performed on references of selected studies to avoid missing the RCTs.

2.2. Study selection

The eligibility criteria to select the studies were parallel-group RCTs in which consumption of a kind of vitamin D (as supplement or fortified food) was compared with placebo in patients with T2D. Studies with participants in any levels of baseline serum 25OHD were included. All kinds of vitamin D like vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol), calcitriol (1, 25-hydroxyvitaminD3), 1-α-hydroxylated versions of vitamin D, paricalcitol, and doxercalciferol used for intervention were also considered. Studies used co-supplementation were included if the control group did not receive any other kind of co-supplementation. Studies used vitamin D on non-type 2 diabetic or pre-diabetic subjects or diabetic patients with nephropathy were excluded. The meta-analyses outcome were changes from baseline in serum lipid profile (total cholesterol (TC), Low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG)) after the follow up period.

2.3. Quality assessment

The quality of selected RCTs was assessed by modified Jadad score [12]. The intention-to-treat and use of blinded endpoints were also added [13]. The score 1 for "Yes" and 0 for "No" were assigned to each answer; so the range of new scoring system was between 0 and 7. This assessment was used to clarify the probable heterogeneity in the results and to achieve a more specific and precise deductions.

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system was used to evaluate the quality of evidence for each outcome (GRADE pro software version 3.6). The quality of evidence was classified as high, moderate, and low [14].

2.4. Extraction of data

The quality scores and characteristics of selected RCTs comprising number of subjects, vitamin D dose (international unit per day), method of vitamin D application, intervention duration, co-supplementation, mean serum 25OHD (nmol/l) of the subjects are shown in Table 1. To increase the precision, the data was extracted independently by the authors. The longest duration of the interventions was considered. For studies with several vitamin D doses, each dose was considered separately if possible.

2.5. Statistical analyses

Cohen's Kappa statistic was used to assess the inter-reviewers agreement in finding the studies, data extraction, and quality assessment [15,16]. Effect size was extracted from each study using mean and standard deviation for TC, LDL, HDL, and TG before and after the intervention. Un-standardized mean difference and its corresponding 95% confidence interval (CI) was calculated from the effect sizes by using random effects model [17]. Lipid markers were reported in mg/dl. Subgroup analyses were performed based on baseline serum 25OHD, method of vitamin D application, vitamin D doses, and intervention duration. Influence analysis was also used to explore the possible sources of heterogeneity among the studies. The heterogeneity was statistically estimated using Cochran's Q test [18] and *I*-squared (I^2) value (ranged from 0 to 100%) [19,20]. The values $\leq$ 25%, 26–50% and >50% are referred to low, moderate, and high estimates, respectively. The funnel plot, Begg and Mazumdar rank correlation test and Egger test were used to evaluate the publication bias [21]. Statistical analyses were carried out using Stata version 11.2 (Stata Corp, College Station, TX). The differences were considered significant at $P \leq 0.05$.

3. Results

3.1. Study selection and identification

The study selection process is shown in Fig. 1. We found 2220 articles in our systematic search; 697 duplicated records were excluded. After reading the titles and abstracts, 1465 from 1523 records were also excluded because of their irrelevancy to the subject. We identified 58 articles that went through detailed

inspection to find the studies assessing the effects of vitamin D on serum lipid profile. Therefore, 35 articles were excluded and the remaining 23 studies were found to be relevant to the topic. Finally, we enrolled 17 studies in our meta-analysis comparing intervention group (received vitamin D) with control group (received placebo) and excluded 6 records; five studies had not a control group and 1 study had not report the results.

We enrolled the study of Witham et al. [22] (with 2 different vitamin D doses) as 2 different studies, as well as the studies of Nikooyeh et al. [23], and Tabesh et al. [24] (both had an additional intervention group for vitamin D and calcium co-supplementation) which were considered as 2 different studies. Therefore, 20 studies were considered in the meta-analysis. In most studies, participants had baseline serum level of 25OHD <50 nmol/l; however, it raised to >50 nmol/l after the interventions (Table 1).

The agreement percentages among researchers and Cohen's Kappa coefficients in finding the studies, data extraction, and quality assessment of the selected studies were >85% and between 0.8 and 1, respectively, which demonstrates a favorable agreement between inter-reviewers.

3.2. Outcomes analysis

The summary of findings table (Table S1) shows the quality assessment for each outcome. “High” implied that further research is doubtful to change the confidence of estimated effect. “Moderate” implied that further research is likely to have an important effect on the confidence of estimated effect. “Low” implied that further research will probably change the confidence of estimated effect.

3.3. Effect of vitamin D on serum TC

All the studies including 1365 subjects had data on the effect of vitamin D on serum TC [3,22–37]. Results demonstrated that vitamin D significantly reduced TC (−11.67 mg/dl, 95% CI: −19.78 to −3.55, $P = 0.005$, data not shown). There was no publication bias by Begg's funnel plot and Egger's test (Egger's test $P = 0.897$). The between studies heterogeneity was high according to I^2 (97.1%) and Cochrane Q tests ($P < 0.001$). Influence analysis was carried out to find the sources of heterogeneity. Results demonstrated that most of the heterogeneity belonged to the studies of Tabesh et al. [24], Rad et al. [31], and Eftekhari et al. [34]. We, therefore, re-analyzed the data after exclusion of the mentioned studies. The heterogeneity among the studies was clearly reduced ($I^2 = 30.1\%$, $P = 0.123$) and the results demonstrated that vitamin D significantly reduced serum TC (Fig. 2: −3.74 mg/dl, 95% CI: −7.13 to −0.34, $P = 0.031$).

Subgroup analyses were also performed based on baseline serum 25OHD of participants, method of vitamin D provision (supplementation or food fortification), vitamin D dosage, and intervention duration (Table 2). Vitamin D significantly reduced serum TC in subjects with baseline serum levels of 25OHD ≥ 50 nmol/l. Serum TC did not show significant reduction in vitamin D deficient subjects (−2.39 mg/dl, 95% CI: −8.84–4.06, $P = 0.467$). Vitamin D-fortified foods significantly reduced serum TC (−7.31 mg/dl, 95% CI: −14.23 to −0.39, $P = 0.038$), while the result of vitamin D supplementation was not statistically significant. Regarding the dose and the duration of intervention, vitamin D in doses ≤2000 IU per day and in the duration of >12 weeks significantly reduced serum TC in patients with T2D (Table 2).

3.4. Effect of vitamin D on serum TG

The effect of vitamin D on serum TG was assessed in 17 studies with 1271 participants [3,23–34,36,37]. Results showed that vitamin D significantly reduced TG in type 2 diabetic patients (−9.49 mg/dl, 95% CI: −18.86 to −0.12, $P = 0.047$, data not shown). Begg's funnel plot and Egger's test indicated that there was no publication bias among the studies (Egger's test $P = 0.536$). The between studies heterogeneity was high according to I^2 (85.2%) and

Table 1
Characteristics of randomized controlled trials enrolled in the meta-analyses.

Study/year	Quality score[a]	No. of subjects	Vitamin D dose (IU/day)	Method of application	Duration (weeks)	Co-supplementation (Dose mg/d)	Baseline vitamin D[b]	Final vitamin D[b]
Jafari et al., 2016 [3]	5	59	2000	Fortification	12	–	Insufficient	Sufficient
Witham et al., 2010 [22]	5	40	833.33	Supplementation	16	–	Sufficient	Insufficient
Witham et al., 2010 [22]	5	39	1666.67	Supplementation	16	–	Sufficient	Sufficient
Nikooyeh et al., 2011 [23]	5	60	1000	Fortification	12	–	Deficient	Sufficient
Nikooyeh et al., 2011 [23]	5	60	1000	Fortification	12	With calcium (500)	Deficient	Sufficient
Tabesh et al., 2014 [24]	5	59	7142.86	Supplementation	8	–	Deficient	Sufficient
Tabesh et al., 2014 [24]	5	60	7142.86	Supplementation	8	With calcium (1000)	Deficient	Sufficient
Kim et al., 2008 [25]	3	24	1200	Supplementation	12	–	Deficient	Not mentioned
Jorde et al., 2009 [26]	2	32	5714.28	Supplementation	24	–	Insufficient	Sufficient
Shab-Bidar et al., 2011 [27]	5	100	1000	Fortification	12	–	Deficient	Sufficient
Munoz-Aguirre et al., 2015 [28]	6	104	4000	Supplementation	24	–	Insufficient	Sufficient
Shehab et al., 2015 [29]	2	112	7142.86	Supplementation	8	–	Deficient	Insufficient
Breslavsky et al., 2013 [30]	2	46	1000	Supplementation	48	–	Deficient	Sufficient
Yousefi Rad et al., 2014 [31]	3	58	4000	Supplementation	8	–	Deficient	Insufficient
Yiu et al., 2013 [32]	5	100	5000	Supplementation	12	–	Insufficient	Insufficient
Al-Zahrani et al., 2014 [33]	3	183	6428.57	Supplementation	8	–	Deficient	Sufficient
Eftekhari et al., 2014 [34]	3	70	20	Supplementation	12	–	Not mentioned	Not mentioned
Kampmann et al., 2014 [35]	4	15	6500	Supplementation	12	–	Insufficient	Sufficient
Ryu et al., 2014 [36]	5	62	2000	Supplementation	24	With calcium (200)	Deficient	Sufficient
Sadiya et al., 2014 [37]	5	82	4500	Supplementation	24	–	Deficient	Insufficient

[a] Quality score of the studies was assessed by Jadad score.
[b] Defficient, serum 25OHD <50 nmol/l; insufficient, 50 ≤ serum 25OHD <75 nmol/l; sufficient, serum 25OHD ≥75 nmol/l.

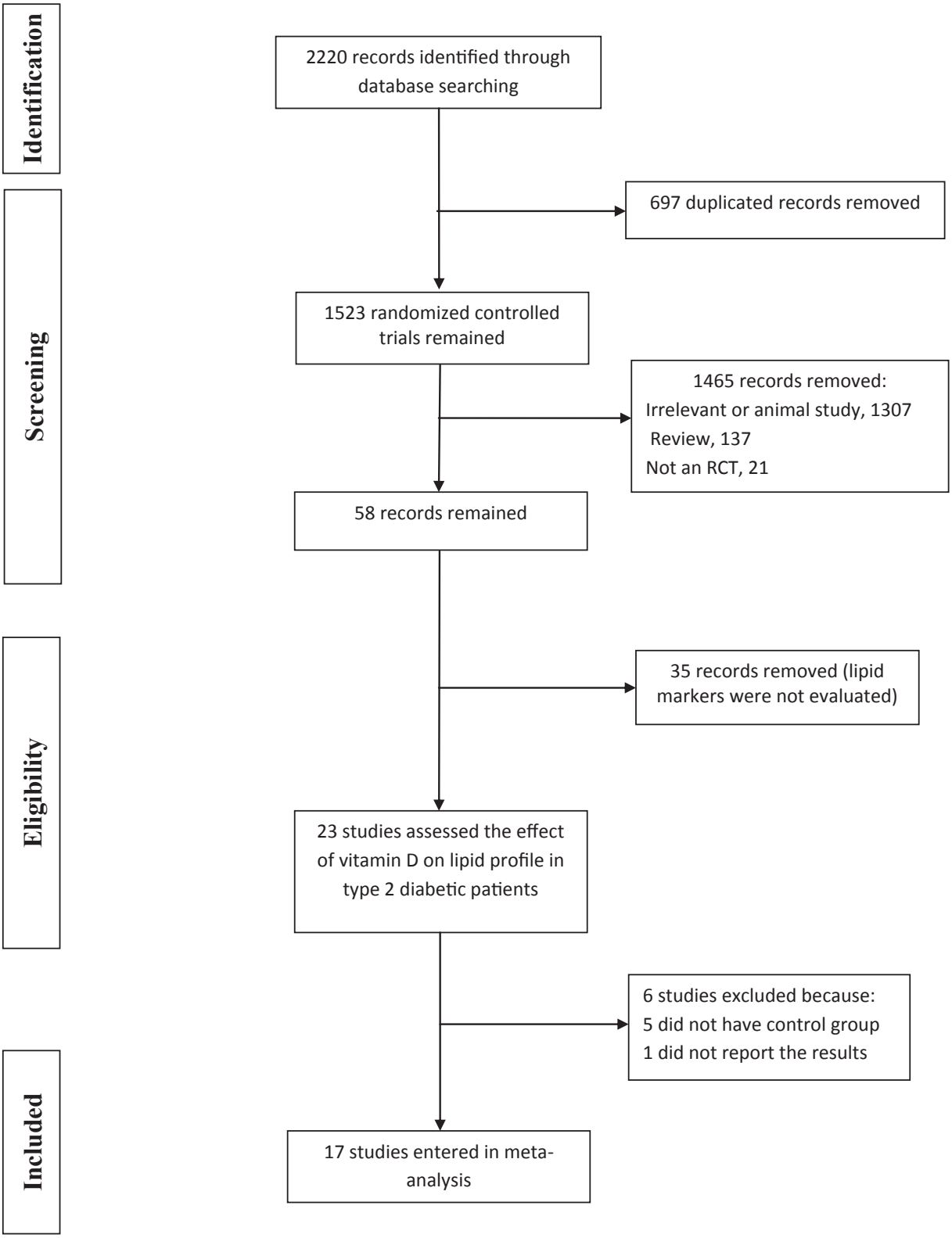

Fig. 1. PRISMA flow diagram of study identification, inclusion, and exclusion.

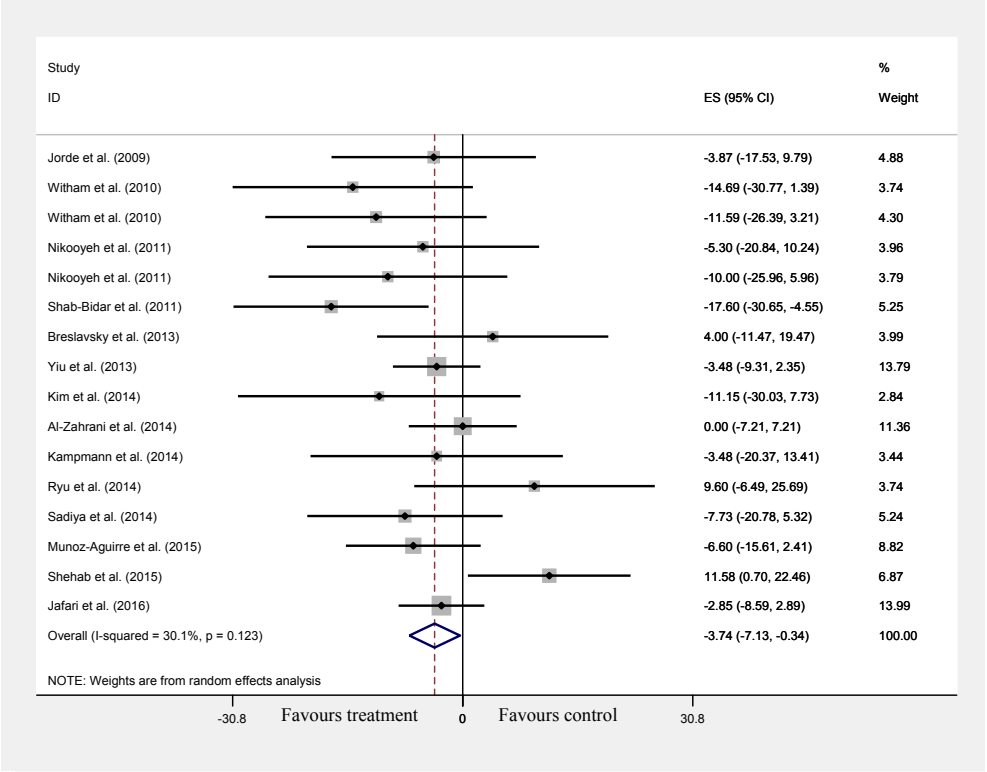

Fig. 2. Forest plot of the effect of vitamin D on total cholesterol.

Cochrane Q tests ($P < 0.001$). Influence analysis revealed that the heterogeneity specifically belonged to the studies mentioned before [24,31,34]. After the exclusion of the studies, the heterogeneity was significantly reduced ($I^2 = 24.6\%$ and Cochrane Q test $P = 0.195$) but the lowering effect of vitamin D on serum TG concentration was not statistically significant (Fig. 3: −4.90 mg/dl, 95% CI: −15.11–5.31, $P = 0.347$).

Subgroup analyses indicated that serum TG reduced significantly in type 2 diabetic patients who received vitamin D ≤ 2000 IU/d (−19.02, 95% CI: −31.04 to −6.99, $P = 0.002$). Vitamin D-fortified foods also significantly reduced the serum TG (−4.90, 95% CI: −15.11 to −5.31, $P = 0.006$); however, the effect of vitamin D on TG did not depend on the baseline serum 25OHD or the duration of vitamin D administration for these patients (Table 3).

3.5. Effect of vitamin D on serum LDL

The meta-analysis of 18 studies with 1286 participants demonstrated that vitamin D did not significantly reduce the LDL (−4.77 mg/dl, 95% CI: −13.78–4.24, $P = 0.300$, data not shown). No publication bias found using Begg's funnel plot and Egger's test (Egger's test $P = 0.222$). However, the between studies heterogeneity was high according to I^2 (98.3%) and Cochrane Q tests ($P < 0.001$). Influence analysis revealed that the heterogeneity belonged to the study of Tabesh et al. [24]. After exclusion of that study, the heterogeneity was significantly reduced ($I^2 = 26.5\%$ and Cochrane Q test $P = 0.156$) and results confirmed the significant lowering effect of vitamin D on LDL in patients with T2D (Fig. 4: −2.55 mg/dl, 95% CI: −4.83 to −0.26, $P = 0.029$).

Table 2
Results of the effect of vitamin D on total cholesterol based on subgroup analyses.

Variable	No. of trials	Effect size (95%CI) mg/dl	*P* Value	I^2 (%)	Q-statistics (*P*)
Baseline serum 25OHD[a]					
Defficient (<50 nmol/l)	9	−2.39 (−8.84, 4.06)	0.467	53.2	0.029
Insufficient (50–75 nmol/l)	5	−3.74 (−7.26, −0.23)	0.037	0	0.975
Sufficient (>75 nmol/l)	2	−13.01 (−23.90, −2.12)	0.019	0	0.781
Method of vitamin D application[a]					
Supplementation	12	−2.51 (−6.55, 1.53)	0.223	30.3	0.150
Food fortification	4	−7.31 (−14.23, −0.39)	0.038	32.2	0.219
Vitamin D dosage[a]					
≤2000 IU/day	9	−6.19 (−11.57, −0.80)	0.024	30.4	0.175
>2000 IU/day	7	−1.82 (−6.16, 2.52)	0.411	28.3	0.212
Intervention duration[a]					
≤12 weeks	9	−3.22 (−7.75, 1.30)	0.162	42.5	0.084
>12 weeks	7	−4.97 (−10.43, 0.48)	0.074	13.5	0.327

[a] Analyses done without the studies of Tabesh et al. [24], Rad et al. [31], and Eftekhari et al. [34].

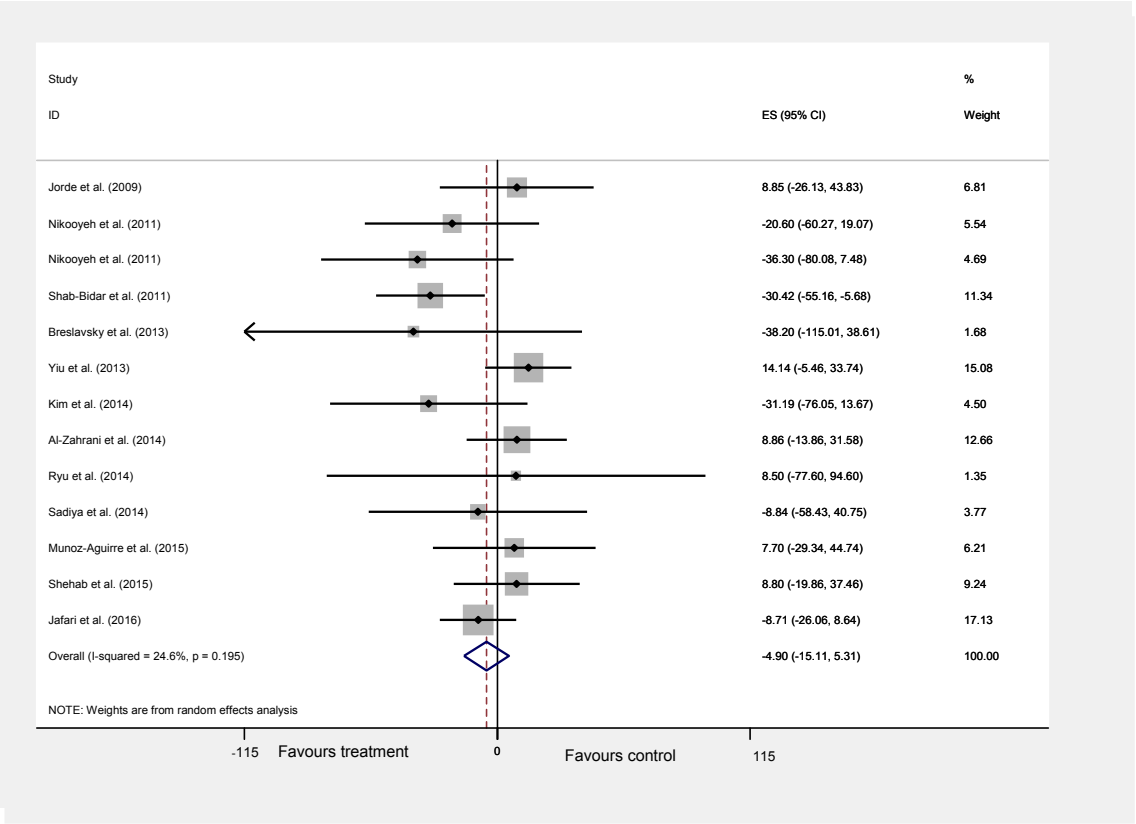

Fig. 3. Forest plot of the effect of vitamin D on triglycerides.

Subgroup analyses showed that vitamin D significantly reduced LDL in type 2 diabetic patients with baseline serum levels of 25OHD ≥ 50 nmol/l. Administration of vitamin D for 12 weeks or less significantly reduced the serum LDL in the patients (−3.09, 95% CI: −5.20 to −0.98, $P = 0.004$). According to the subgroup analyses, vitamin D dose or method of its application did not significantly reduce serum LDL (Table 4).

3.6. Effect of vitamin D on serum HDL

The meta-analysis of 18 RCTs with 1286 type 2 diabetic patients showed that vitamin D did not significantly change serum HDL in patients with T2D (1.92 mg/dl, 95% CI: −2.45–6.29, $P = 0.390$, data not shown). There was no publication bias found by Begg's funnel plot and Egger's test (Egger's test $P = 0.360$). The between studies heterogeneity was high according to I^2 (98.8%) and Cochrane Q tests ($P < 0.001$). Influence analysis revealed that the heterogeneity belonged to the study of Tabesh et al. [24]. The analysis was re-performed after excluding that study, showing that vitamin D slightly but significantly decreased the serum HDL (Fig. 5: −0.72 mg/dl, 95% CI: −1.27 to −0.17, $P = 0.010$). The heterogeneity was also significantly reduced ($I^2 = 0\%$ and Cochrane Q test $P = 0.765$).

Subgroup analyses showed that vitamin D supplementation decreased the serum HDL in type 2 diabetic patients with sufficient serum levels of 25OHD (−1.20, 95% CI: −1.95 to −0.44, $P = 0.002$), particularly when the intervention duration was ≤12 weeks (−0.71, 95% CI: −1.33 to −0.083, $P = 0.026$). However, vitamin D-fortified

Table 3
Results of the effect of vitamin D on triglycerides based on subgroup analyses.

Variable	No. of trials	Effect size (95%CI) mg/dl	*P* Value	I^2 (%)	Q-statistics (*P*)
Baseline serum 25OHD[a]					
Defficient (<50 nmol/l)	9	−12.29 (−26.30, 1.85)	0.089	20.9	0.257
Insufficient (50–75 nmol/l)	4	2.94 (−9.08, 14.97)	0.631	5.00	0.368
Sufficient (>75 nmol/l)	0	–	–	–	–
Method of vitamin D application[a]					
Supplementation	9	6.24 (−4.60, 17.08)	0.259	0	0.752
Food fortification	4	−4.90 (−15.11, −5.31)	0.006	0	0.431
Vitamin D dosage[a]					
≤2000 IU/day	7	−19.02 (−31.05, −6.99)	0.002	0	0.718
>2000 IU/day	6	9.59 (−1.80, 20.98)	0.099	0	0.980
Intervention duration[a]					
≤12 weeks	8	−7.49 (−21.13, 6.14)	0.281	50.3	0.050
>12 weeks	5	1.74 (−19.31, 22.78)	0.871	0	0.827

[a] Analyses done without the studies of Tabesh et al. [24], Rad et al. [31], and Eftekhari et al. [34].

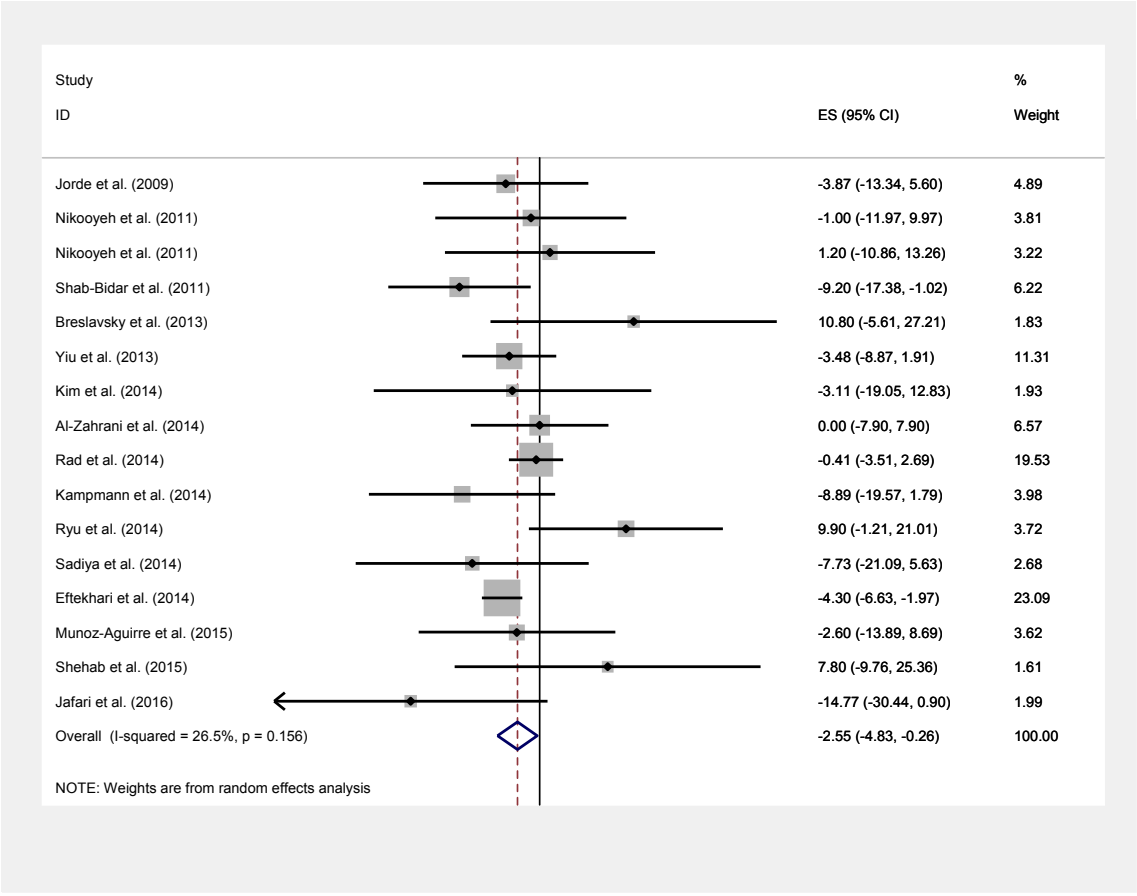

Fig. 4. Forest plot of the effect of vitamin D on LDL.

food improved serum HDL in these patients but the results was not statistically significant (Table 5).

4. Discussion

Diabetes-related dyslipidemia (hypertriglyceridemia, low-serum HDL, elevated serum TC, and cholesterol-rich lipoproteins) is prevalent and can lead to atherosclerosis. Statins are the most common drugs used for treatment of these disorders in patients with T2D. However, the problem may have been incompletely resolved, so the adjuvant therapies are required as well.

Obvious correlations are reported between higher levels of serum 25OHD and lower prevalence of diabetes, hypertension and cardiovascular diseases [3]. Observational studies reported an inverse correlation between higher levels of serum 25OHD and lower levels of total serum cholesterol, LDL, TG, and higher levels of serum HDL [10]; but the results of RCTs to evaluate the effects of vitamin D on lipid profile are conflicting. The exact mechanism by which vitamin D affects lipid markers is not clear.

The overall results of the current meta-analyses revealed that vitamin D improved serum levels of TC, TG, and LDL, while changes in serum HDL were negligible. It could be estimated that serum TC of type 2 diabetic patients received vitamin D, reduce about 4 mg/

Table 4
Results of the effect of vitamin D on LDL cholesterol based on subgroup analyses.

Variable	No. of trials	Effect size (95%CI) mg/dl	*P* Value	I^2 (%)	Q-statistics (*P*)
Baseline serum 25OHD[a]					
Defficient (<50 nmol/l)	10	−0.40 (−3.81, 3.02)	0.820	23.2	0.229
Insufficient (50–75 nmol/l)	5	−4.85 (−8.73, −0.96)	0.014	0	0.639
Sufficient (>75 nmol/l)	1	−4.30 (−6.63, −1.97)	0.0001	0	0
Method of vitamin D application[a]					
Supplementation	12	−2.01 (−4.44, 0.42)	0.105	27.7	0.172
Food fortification	4	−5.61 (−12.00, 0.77)	0.085	24.1	0.267
Vitamin D dosage[a]					
≤2000 IU/day	8	−2.13 (−6.94, 2.67)	0.384	48.3	0.065
>2000 IU/day	8	−1.68 (−3.97, 0.60)	0.149	0	0.643
Intervention duration[a]					
≤12 weeks	11	−3.09 (−5.20, −0.98)	0.004	16.9	0.283
>12 weeks	5	0.68 (−6.31, 7.68)	0.848	41.4	0.145

[a] Analyses done without the study of Tabesh et al. [24].

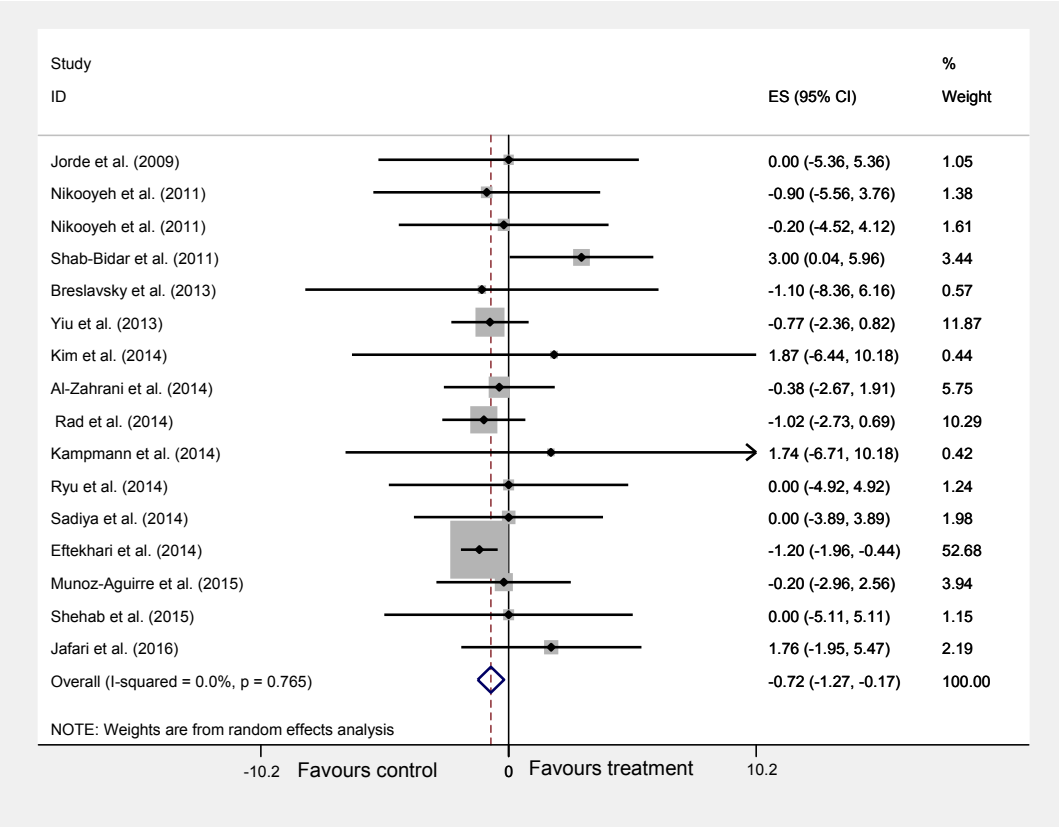

Fig. 5. Forest plot of the effect of vitamin D on HDL.

Table 5
Results of the effect of vitamin D on HDL cholesterol based on subgroup analyses.

Variable	No. of trials	Effect size (95%CI) mg/dl	*P* Value	I^2 (%)	Q-statistics (*P*)
Baseline serum 25OHD[a]					
Defficient (<50 nmol/l)	10	−0.13 (−1.17, 0.90)	0.800	0	0.776
Insufficient (50–75 nmol/l)	5	0.27 (−1.52, 0.97)	0.665	0	0.780
Sufficient (>75 nmol/l)	1	−1.20 (−1.95, −0.44)	0.002	0	0
Method of vitamin D application[a]					
Supplementation	12	−0.93 (−1.50, −0.35)	0.001	0	0.996
Food fortification	4	1.46 (−0.40, 3.33)	0.125	0	0.454
Vitamin D dosage[a]					
≤2000 IU/day	8	0.09 (−1.34, 1.53)	0.897	28.8	0.198
>2000 IU/day	8	0.60 (−1.50, 0.31)	0.195	0	0.997
Intervention duration[a]					
≤12 weeks	11	−0.71 (−1.33, −0.083)	0.026	3.40	0.410
>12 weeks	5	−0.16 (−2.01, 1.69)	0.865	0	0.999

[a] Analyses done without the study of Tabesh et al. [24].

dl. Subgroup analyses revealed that the best results for serum TC achieved when baseline serum levels of 25OHD was >75 nmol/l (~13 mg/dl reduction); hence serum levels of 25OHD > 75 nmol/l might be optimal to have beneficial effect on serum TC. It is also suggested that administration of vitamin D ≤ 2000 IU per day is enough to reduce serum TC (~6 mg/dl reduction). The effects of vitamin D on serum TC seems to be more effective in subjects who received a vitamin D-fortified food than those who received supplements. Pooling the data from RCTs demonstrated that vitamin D administration for a mean period of 12 weeks, reduced serum LDL (~3–4 mg/dl) in type 2 diabetic patients with baseline serum levels of 25OHD > 50 nmol/l.

The serum TC concentration is affected by cholesterol absorption from the gut and endogenous biosynthesis of cells. Changes in serum campesterol and lathosterol as cholesterol precursors, indicate the amount of cholesterol absorption and endogenous production, respectively. The possible role of vitamin D on intestinal cholesterol absorption or endogenous production is not clear and needs further investigations. Kane et al. [38] reported the reduction of serum campesterol in statin-treated subjects who received vitamin D. They suggested that vitamin D might reduce intestinal cholesterol absorption. Vitamin D can also prevent atherosclerosis by reduction of foam cell formation and decrease LDL deposition in macrophages of patients with T2D [39].

It has been demonstrated that vitamin D increases lipoprotein lipase (LPL) gene expression in muscles and adipose tissue. The activation of LPL increases the clearance of circulating lipoprotein particles and modifies the lipid profile in favor of reducing

atherosclerosis. The most obvious effects of LPL are reduction in serum TG and increase in serum HDL [40]. Hypertriglyceridemia, low serum HDL, and decreased adipose tissue LPL activity are common in diabetic patients. Therefore, vitamin D administration could have benefits for these subjects. Although pooling the data from RCTs showed that vitamin D did not significantly reduce serum TG, subgroup analyses demonstrated that administration of vitamin D $\leq$ 2000 IU per day significantly reduced serum TG (~19 mg/dl) in patients with T2D. Patients consuming a vitamin D-fortified food showed the best results, which might be because those taking supplements had been advised to take them with fat containing foods, to improve its absorption.

Our meta-analysis found a very slight but significant decrease in serum HDL (<1 mg/dl) in type 2 diabetic patients who received vitamin D. Subjects with sufficient baseline serum vitamin D, or those who received vitamin D as supplements for 12 weeks or less, even showed detrimental results (~1 mg/dl reduction). More studies on vitamin D-deficient patients with longer durations are needed to clarify these results. As mentioned before, it seems that vitamin D can increase serum HDL by activating the LPL, but other mechanisms by which vitamin D affects serum HDL are not clear. Studies in vitamin D-receptor knockout mice revealed higher HDL and hepatic apo A-1 mRNA expression compare to wild type. Vitamin D experimental studies on cultured hepatocytes supported these findings [41]. But human studies have conflicting results; a positive relationship between plasma apo A-1 and HDL is reported with serum 25OHD, while in the small intestine and hepatocytes an inverse association is suggested [42].

The current meta-analyses demonstrate that, overall, vitamin D-fortification has more desirable effect on lipid profile in patients with T2D comparing to vitamin D-supplementation. Considering the fact that diabetic patients usually used a great deal of medicines, the compliance of subjects receiving vitamin D as a fortified food may be better than that of those given vitamin D supplements. It is also represented that vitamin D $\leq$ 2000 IU/day and in an intervention duration of $\leq$12 weeks have more beneficial effects on lipid profile compare to higher doses and longer durations. Considering the possible role of vitamin D as an adjuvant treatment for dyslipidemia, it may be due to the fact that patients were not in the same levels of lipid control.

Influence analyses indicated that the major sources of heterogeneity in results were due to studies of Tabesh et al. [24], Eftekhari et al. [34], and Rad et al. [31]. We decided to conduct the meta-analyses after the exclusion of the mentioned studies. The other sources of heterogeneity were the variations in the study population, geographical latitudes, gender, the health status of patients, and quality of the studies. We also performed subgroup analyses to represent the effect of vitamin D on lipid markers more clearly.

Wang et al. [10] conducted a meta-analysis to evaluate the effect of vitamin D on lipid profile of subjects with different health conditions. They concluded that vitamin D supplementation increased LDL, but does not significantly affect serum TC, HDL, and TG. Our different results might be due to the fact that we just evaluate type 2 diabetic patients. It is also possible that lipid-lowering effects of vitamin D were different based on the study population and might be seen more apparently in patients with metabolic disorders such as diabetes and cardiovascular diseases as well as having hypercholesterolemia or other abnormal lipid metabolism.

According to GRADE, all lipid markers as outcomes were appraised as moderate quality. It means that further research may change the estimated effects. Some strengths of the current study are as follows: the design of the study, conducting the analyses on a specific population (type 2 diabetic subjects) instead of pooling populations with different health conditions, and subgroup analyses. This study is the first meta-analysis assessing the effect of vitamin D on lipid profile in patients with T2D. There are also some limitations: evaluating the effects of vitamin D with calcium co-supplementation on lipid markers was not possible due to the small number of studies on the subject, lipid markers had been assessed by methods with different accuracy, patients might have been in different status of diabetes, and the history of using anti-dyslipidemic drugs (such as statins) was not clear.

5. Conclusion

This study demonstrated that vitamin D had minor effects on lipid profile of type 2 diabetic patients. Therefore, vitamin D cannot be considered as a main therapeutic agent for dyslipidemia, but it could be used as an adjuvant therapy along with the other treatments for those patients. Vitamin D dosage and the duration of intervention might influence the effect of vitamin D on lipid profile. Type 2 diabetic patients with different baseline serum 25OHD showed different results. The current meta-analyses also demonstrated that vitamin D-fortification has more desirable effect on lipid profile of patients with T2D, as compared to the vitamin D-supplementation.

Conflict of interest

The authors disclose no conflicts of interest.

Statement of authorship

The responsibility of authors was as follow: TJ and AAF were involved in literature search, data extracting, data synthesis, statistical analysis, and quality assessing of the articles. AB was involved in literature search. TJ supervised the study. Authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.03.001.

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